Validation Issues and Genetically Modified Mouse Models

Richard A. Becker, Ph.D. DABT
American Chemistry Council

March 2004

Validation is Needed

- PUBLIC LAW 106–545—DEC. 19, 2000

(c) TEST METHOD VALIDATION.—Each Federal agency carrying out a program described in subsection (a) [requires or recommends acute or chronic toxicological testing] shall ensure that any new or revised acute or chronic toxicity test method, including animal test methods and alternatives, is determined to be valid for its proposed use prior to requiring, recommending, or encouraging the application of such test method.

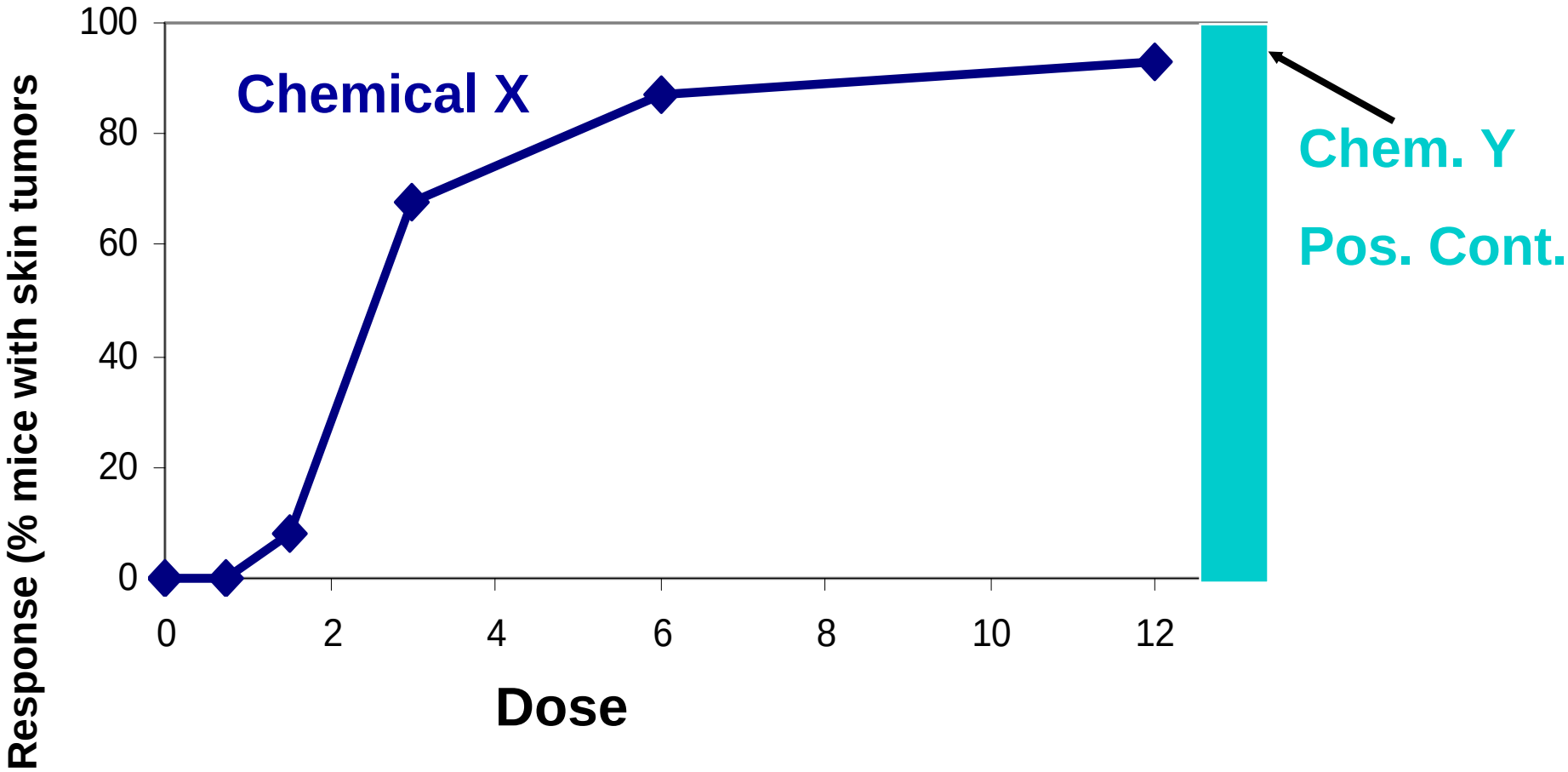
Validation
Answers the Questions Needed for Use of Test Results

- What is the intended purpose of the method?
- Have relevance & reliability been established?
  - Across specific classes of compounds
  - Dose levels
- Is there sufficient data to judge performance compared to the method it is intended to replace?
- How are the results to be interpreted & applied?

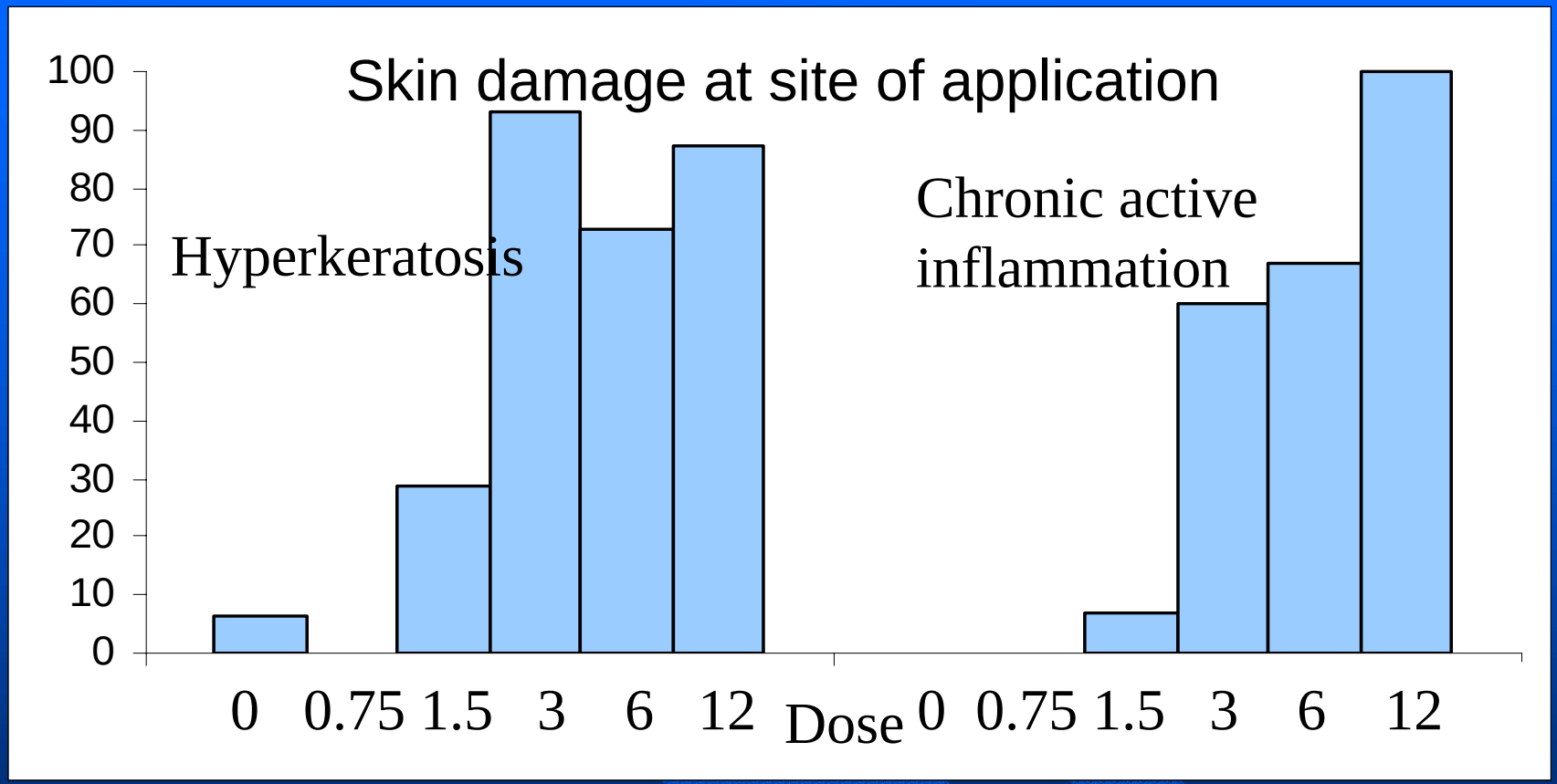
Transgenics

- Already- considerable work has been done
- But key & critical questions have not been addressed because the work to date has not been organized specifically for a methods validation review
- ICCVAM can bring clarity to the situation

Dose Response Chemical X in TgAC assay (females)

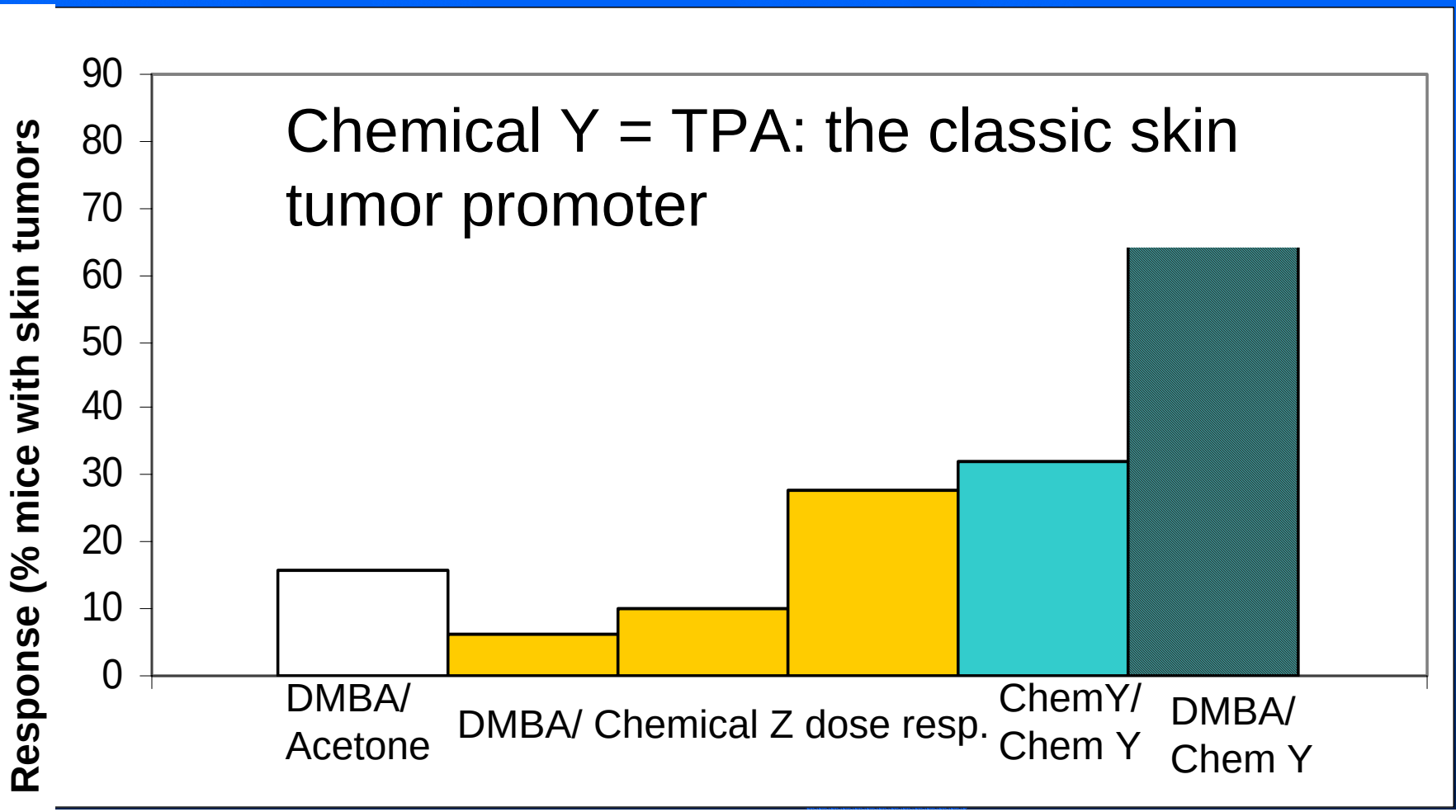


Dose Response Chemical X in TgAC assay (females)



Surgically inflicted full-thickness incisions 3 cm long yielded four to six papillomas per Tg.AC mouse by 5 wk after wounding. The wound repair response leads to the transcriptional activation and continued expression of the v-Ha-*ras* transgene in specific cells in the skin, which alters normal epithelial differentiation and ultimately results in neoplastic growth. Molecular Carcinogenesis Volume 20, 108-114, 1997

Chemical Y in Classic Mouse Skin Painting Study (Initiation + Promotion (males))



Conclusion: Chemical Z considered to be a weak skin tumor promoter

Drawing Conclusions from Transgenic Assays?

- "There is ["clear", "equivocal", "some", "no", "inadequate"] evidence of activity in the Tg.AC transgenic mouse model. The model cannot be used for [or is of extremely limited utility for] substances (doses) which produce skin irritation or damage. The TgAC transgenic mouse model provides qualitative information on biological potential and mode of action, but results of this assay alone cannot be used to extrapolate (either qualitatively or quantitatively) to potential hazards to humans."

Recommendations

- Initiate a Validation review by ICCVAM
- To cover
  - Purpose of method(s)
  - Relevance & Reliability assessments
    - » Dose considerations
    - » Classes of compounds
    - » Strengths/limitations
- Interpretation of results - Is there sufficient data to judge performance compared to the method it is intended to replace?